The Pathogenesis of Extraintestinal Manifestations: Implications for IBD Research, Diagnosis, and Therapy

Hedin, C R H ; Vavricka, S R ; Stagg, A J ; Schoepfer, A ; Raine, T ; Puig, L ; Pleyer, U ; Navarini, A ; van der Meulen-de Jong, A E ; Maul, J ; Katsanos, K ; Kagramanova, A ; Greuter, T ; González-Lama, Y ; van Gaalen, F ; Ellul, P ; Burisch, J ; Bettenworth, D ; Becker, M D ; Bamias, G ; Rieder, F

Abstract: This article reports on the sixth scientific workshop of the European Crohn's and Colitis Organisation [ECCO] on the pathogenesis of extraintestinal manifestations [EIMs] in inflammatory bowel disease [IBD]. This paper has been drafted by 15 ECCO members and 6 external experts [in rheumatology, dermatology, ophthalmology, and immunology] from 10 European countries and the USA. Within the workshop, contributors formed subgroups to address specific areas. Following a comprehensive literature search, the supporting text was finalized under the leadership of the heads of the working groups before being integrated by the group consensus leaders.

DOI: https://doi.org/10.1093/ecco-jcc/jjy191

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Hedin, CRH,[1] Vavricka SR,[2] Stagg, A,[3] Schoepfer A,[4] Raine, T,[5] Puig L,[6] Pleyer U,[7] Navarini A,[8] van der Meulen A,[9] Maul J,[10] Katsanos K,[11] Kagramanova A,[12] Greuter T,[13,14] Gonzalez Lama Y,[15] van Gaalen F,[16] Ellul P,[17] Burisch J,[18,19] Bettenworth D,[20] Becker MD,[21] Bamias, G,[22] Rieder, F.[23]

1. Gastroenterology unit, Patient Area Gastroenterology, Dermatovenereology and Rheumatology, Karolinska University Hospital, Stockholm, Sweden.

2. Centre for Gastroenterology and Hepatology, Zurich, Switzerland.

3. Barts and The London, Queen Mary's School of Medicine and Dentistry, Centre for Immunobiology, London, United Kingdom.

4. FMH Internal Medicine, Gastroenterology and Hepatology, Department of gastroenterology and hepatology, Vaud University Hospital Center / CHUV, Lausanne, France.

5. Department of Gastroenterology, Addenbrooke's Hospital, Cambridge University teaching hospitals NHS foundation trust, Cambridge, United Kingdom.

6. Dept. of Dermatology, Hospital de la Santa Creu i Sant Pau. Universitat Autònoma de Barcelona. Barcelona, Catalonia, Spain.

7. University Eye Clinic, Uveitis Center, Charité - Universitätsmedizin Berlin.

8. University Hospital Zurich, Department of Dermatology, Zurich, Switzerland

9. Leiden University Medical Center (LUMC)

10. Gastroenterology at Bayerischer Platz, Berlin, Germany.

11. Division of Gastroenterology, Department of Internal Medicine, Medical School, University of Ioannina School of Medical Sciences, 45110 Ioannina, Greece.

12. The Loginov Moscow Clinical Scientific Centre, IBD Department

13. Division of Gastroenterology and Hepatology, University Hospital Zurich, Zurich, Switzerland

14. Gastroenterology Research Unit, Mayo Clinic, Rochester, MN, USA.

15. Intestinal Inflammatory Disease Unit / IBD Unit, Gastroenterology and Hepatology Service / Gastroenterology and Hepatology Dpt., Puerta de Hierro University Hospital, Majadahonda, Madrid, Spain.
16. Leiden University Medical Center (LUMC), Department of Rheumatology, Leiden, Netherlands.
17. Department of Medicine, Division of Gastroenterology, Mater Dei Hospital, Malta.
18. Center for Clinical Research and Prevention, Bispebjerg and Frederiksberg Hospital, University of Copenhagen, Denmark
19 Abdominal center K, medical section, Bispebjerg and Frederiksberg Hospital, University of Copenhagen, Denmark
20. Department of Medicine B, Gastroenterology and Hepatology, University Hospital Münster, Münster, Germany
21. Triemli Hospital, Department of Ophthalmology, Zurich, Switzerland.
22. National and Kapodistrian University of Athens, GI Unit, 3rd Academic Dpt. Of Internal Medicine, Sotiria Hospital, Athens, Greece.
23. Department of Gastroenterology, Hepatology and Nutrition; Digestive Diseases and Surgery Institute, Cleveland Clinic Foundation, Cleveland, OH, USA.

Stephan Vavricka: stephan.vavricka@usz.ch
Andrea van der Meulen: ae.meulen@lumc.nl
Floris van Gaalen: F.A.van_Gaalen@lumc.nl
Andy Stagg: a.stagg@qmul.ac.uk
Alain Schoepfer: Alain.Schoepfer@chuv.ch
Lluis Puig Sanz: LPuig@santpau.cat
Tim Raine: timraine@doctors.net.uk
Uwe Pleyer: uwe.pleyer@charite.de
Alexander Navarini: Alexander.Navarini@usz.ch
Jochen Maul: jochen.maul@charite.de
Yago Gonzalez Lama: ygonzalezlama@telefonica.net
Kostas Katsanos: khkostas@hotmail.com
Anna Kagramanova: kagramanova@me.com
Thomas Greuter: TH_GREUTER@BLUEWIN.CH

Pierre Ellul: ellul.pierre@gmail.com

Johan Burisch: burisch@gmail.com

Dominik Bettenworth: dominik.bettenworth@ukmuenster.de

Matthias Becker: Matthias.Becker@triemli.zuerich.ch

Giorgos Bamias: gbamias@gmail.com

Florian Rieder: riederf@ccf.org

Author contributions

ALL AUTHORS: This article is a result of a joint scientific workshop activity. Hence, all authors participated sufficiently, intellectually or practically, in the work to take public responsibility for the content of the article, including the conception, design, data interpretation and writing of the article. The final version of the article was approved by all authors.

Short title: EIM pathogenesis in IBD

Non-standard abbreviations:

CD	Crohn's disease
IBD	Inflammatory bowel disease
TNF	Tumour necrosis factor
PSC	Primary sclerosing cholangitis

Correspondence:

Dr. Charlotte Hedin

PO Gastroenterology, Dermatovenerology and Rheumatology

Inflammation and Infection Theme

Karolinska University Hospital

171 76 Solna

Sweden

Conference presentations: ECCO 2018

Funding

No study sponsors had any involvement in study design, data collection, interpretation or writing of the manuscript

Conflict of interest

Charlotte Hedin: CH has received consulting fees or lecture honoraria from Abbvie, Ferring, Janssen, Pfizer, Takeda and research funding from Takeda.

Stephan Vavricka: SRV has served as consultant/received speaker fees from Abbvie, Janssen, MSD, Takeda, Falk, Ferring, UCB, Tillotts, and Vifor

Andrea van der Meulen: AM has served as consultant for Takeda and received a research grant from Takeda.

Floris van Gaalen: FvG provided consultancy for MSD, Novartis, Pfizer and Abbvie

Andy Stagg: AS has received research funding from Takeda

Alain Schoepfer: AS received consultancy and/or speaker fees from Abbvie, Adare, Falk, MSD, Pfizer, Takeda, UCB, Receptos, and Regeneron

Lluis Puig: has received research/educational grants and/or speaker/consultation fees from Abbvie, Almirall, Amgen, Boehringer, Baxalta, Biogen, Boehringer, Ingelheim, Celgene, Gebro, Janssen, Leo-Pharma, Lilly, Merck-Serono, MSD, Mylan, Novartis, Pfizer, Regeneron, Roche, Sandoz, Sanofi, UCB

Tim Raine: TR has received research/educational grants and/or speaker/consultation fees from Abbvie, Gilead, GSK, Janssen, MSD, Novartis, Pfizer, Sandoz and Takeda

Uwe Pleyer: UP has received research/educational grants and/or speaker/consultation fees from Abbvie, Alcon, Allergan, Novartis, Santen, Thea

Alexander Navarini: AK declares no conflicts of interest

Jochen Maul: JM has provided consultancy and received payment for lectures from Abbvie, Falk Foundation, Janssen, MSD, Pfizer and Takeda.

Yago Gonzalez Lama: YGL has served as consultant for Abbvie, Janssen and Takeda and has received research grants and speaker fees from Abbvie, MSD and Takeda.

Kostas Katsanos: K.H.K received honoraria for consulting services (educational services, scientific articles, participation in Advisory Boards, clinical trials, other) from AbbVie, ENORASIS, Ferring, Genesis, Grifols S.A., JANSSEN, MSD, Shire and Takeda.

Anna Kagramanova: AK declares no conflicts of interest

Thomas Greuter: TG is a consultant for Sanofi Aventis, received a travel grant from Falk Pharma GmbH and Vifor, and an unrestricted research grant from Novartis.

Pierre Ellul: PE has received educational grants from Abbvie and MSD.

Johan Burisch: JB has received personal fees from AbbVie, Janssen-Cilag, Celgene, MSD, and Pfizer, grants and personal fees from Takeda, outside the submitted work.

Dominik Bettenworth: DB has served as consultant for Abbvie, Janssen, Pharmacosmos, Takeda and Tillots and has received speaker fees from Abbvie, Falk, Ferring, MSD, Pfizer, Roche, Takeda and Vifor.

Matthias Becker: MDB received research support from Novartis and Bayer, has received speaker fees from Allergan and Zeiss and has provided consultancy to Allergan, Alcon, Santen, Zeiss and AbbVie.

Giorgos Bamias: GB has received consulting fees or lecture honoraria from Pfizer, Ferring, Aenorasis, Jannsen, Takeda, Cellgene, MSD and Abbvie and research grants from Takeda.

Florian Rieder: FR is on the advisory board for AbbVie, Celgene, Receptos, Thetis, Pfizer, Takeda and UCB, consultant to Samsung, UCB, Celgene, Cowen, Pliant, Boehringer-Ingelheim, Helmsley, RedX, Thetis and Roche and on the speakers' bureau of AbbVie.

MANUSCRIPT BODY

This article reports on the sixth scientific workshop of the European Crohn's and Colitis Organisation (ECCO) on the pathogenesis of extraintestinal manifestations (EIM) in inflammatory bowel disease (IBD). This paper has been drafted by 15 ECCO members and 6 external experts (rheumatology, dermatology, ophthalmology and immunology) from 10 European countries and the USA. Within the workshop contributors formed subgroups to address specific areas. Following a comprehensive literature search, the supporting text was finalised under the leadership of the heads of the working groups before being integrated by the group consensus leaders.

INTRODUCTION

Up to 50% of IBD patients experience at least one extraintestinal manifestation (EIM).[1] The pathogenic mechanisms of EIM are not clearly defined. Unravelling these pathways has the potential to enhance our understanding of the pathogenesis not only of EIM but also of IBD overall. Defining pathogenic pathways in EIM is challenging due to the lack of consistent criteria for diagnosis and difficulty in distinguishing drug-induced extraintestinal pathologies from EIM. Optimising treatment may also be problematic. For many EIMs commonly accepted definitions and high quality evidence supporting different treatment strategies are lacking.[2] Therefore, there is a great need for both basic science studies and clinical trials to understand pathogenesis and determine optimal treatment of EIM. The first ECCO European Evidence-based consensus on EIM in IBD provided an authoritative guideline for the clinical management of EIM.[2] The current article seeks to complement and extend the clinical guideline by identifying frontiers and open questions for clinical research.

DEFINITION

In order to standardize systematic inclusion of patients in scientific and clinical studies and align outcome measures to ensure clarity across the scientific literature, widely agreed upon definitions of the pathology being studied are critical. In order to provide a frame of

reference for scientific discourse the expert panel suggests the following *mechanistic* definition of what constitutes an EIM:

"An inflammatory pathology in a patient with IBD that is located outside the gut whose pathogenesis is either dependent on extension/translocation of immune responses from the intestine, or is an independent inflammatory event perpetuated by IBD or that shares a common environmental or genetic predisposition with IBD."

A wide range of extraintestinal pathologies are associated with IBD, however not all of these would be considered to be true EIM according to the definition above. The panel proposes that current data supports pathologies listed in the first column of **Table 1** as true EIM, with other pathologies classified as associated auto-immune conditions or complications of IBD and its treatment. The distinction between these categories can be imprecise and overlap likely exists; it is probable that with future new data some pathologies will be re-classified. For the purpose of this review the panel focussed on true EIM as described by the definition above.

BASIC MECHANISMS OF EIM

Immunological mechanisms

The potentially diverse immune mechanisms that underlie EIM are poorly defined. We discuss two distinct theories that mechanistically link inflammation in the intestine and at other sites. First, EIM arise from an extension of antigen specific immune responses from the intestine to non-intestinal sites. Second, EIM are independent inflammatory events initiated or perpetuated by presence of IBD or by shared genetic or environmental risk factors in the host. These mechanisms are not mutually exclusive and may contribute to varying degrees in different EIM (**Figure 1**).

Extension of immune responses from the intestine

Ectopic expression of gut-specific chemokines and adhesion molecules:

Abnormal patterns of lymphocyte homing in IBD may contribute to EIM[3]. Expression of the vascular addressin MAdCAM-1 is normally restricted to intestinal tissue and, in the context

of specific chemokine signals, enables gut tropic T cells that express α4β7 integrin to traffic selectively to the intestinal mucosa. Additional tropism for the small intestine comes from the chemokine CCL25 attracting lymphocytes expressing its receptor CCR9. Ectopic expression of both chemokines and adhesion molecules can occur in IBD[4], and may facilitate trafficking of inflammatory T cells to extraintestinal sites. The best supporting evidence comes from IBD associated primary sclerosing cholangitis (PSC). Ectopic expression of both MAdCAM-1 and CCL25 has been demonstrated in the vascular endothelium of the portal tract.[5, 6] One fifth of the infiltrating T cells co-express CCR9 and α4β7, whereas the frequency of these cells is low in other forms of liver inflammation, indicating an important role for these molecules in recruitment of inflammatory lymphocytes in PSC.[6] While attractive to propose ectopic expression of gut-associated addressins at extraintestinal sites as a logical mechanism for EIM, evidence that this occurs in organs other than liver is lacking. However, co-expression of α4β7 with cutaneous leukocyte antigen (CLA), (implicated in homing to the skin), by some blood T cells from IBD patients[7], may indicate that gut generated effector cells can acquire both gut and skin tropism.

T cell trafficking driven by non-specific adhesion molecules:

Upregulation of inflammation-associated adhesion molecules and chemokines that lack tissue restriction may also enable capture of effector cells facilitating their recruitment into non-intestinal sites. Gut leukocytes from IBD patients are able to bind to the synovial membrane, using a repertoire of adhesion molecules[8], but mainly using endothelial vascular adhesion protein 1 (VAP-1)[9]. VAP-1 also plays a role in transmigration of lymphocytes across hepatic endothelium and its expression is upregulated by inflammation.[10, 11] T cells from intestinal mucosa of IBD patients express chemokine receptors, such as CXCR3 and CCR5,[12, 13] that may contribute to their ability to enter other tissues. Low-grade inflammation, injury or mechanical stress at extraintestinal sites (as implicated in the pathogenesis of spondyloarthritis (SpA)[14] and pyoderma gangrenosum, where this phenomenon is termed pathergy) may nucleate the recruitment of gut-generated effector cells and further enhance the inflammatory process.

Microbial antigen translocation and/or cross-reactivity:

Models of EIM that invoke trafficking of gut effector T cells raise the question as to whether this process is dependent on antigen specific reactivation at non-intestinal sites and if so,

what the antigen may be. Antigens derived from the gut microbiota are believed to be key targets for intestinal effector T cells in IBD and transport of these antigens to the liver via the portal circulation may activate such cells localised here via α4β7-MAdCAM-1 interactions and other pathways. The presence of distinct gut microbiota in IBD patients with PSC[15-17] may suggest specific bacterial antigens. At other sites, cells may be reactivated by cross-reactive components of the resident microbiota or host antigens. Molecular mimicry, in the form of peptide sequences common between enteric bacteria and host MHC molecules has been reported[18, 19] although the pathologic significance of this is unclear. In mice, retina-specific T cells that cause uveitis require activation in the gut by a microbiota dependent signal, most likely a cross reactive bacterial antigen,[20] providing evidence for a direct link between gut microbiota, recognition of self-antigens and inflammation at a non-intestinal site. Indeed, leukocyte trafficking between the gut and the eye has been demonstrated in experimental models of autoimmune uveitis.[21] However, the antigen specificity of T cells responsible for EIM in humans has never been defined.

Circulating antibodies:

Circulating antibodies could extend intestinal immune responses to additional sites and immune complex mediated inflammation has been proposed to contribute to certain EIM[22]. Autoantibodies reactive to colonic proteins have been identified in patients with IBD[23, 24] and, using monoclonal antibodies, epitopes shared between human colon and tissues such as eyes, joints, skin and biliary epithelium have been identified.[25-27] However, clear evidence of a causative role for antibodies or immune complexes in the pathogenesis of EIM in IBD patients is lacking.

EIM as independent inflammatory events

A shift in inflammatory tone favours the development of EIM:

An alternative explanation for EIM would see them as independent inflammatory events sharing common genetic[28] or environmental[29] risk factors with IBD. The presence of intestinal inflammation and/or microbial dysbiosis in individuals with IBD might further increase the risk of developing extraintestinal inflammation through modulation of inflammatory 'tone', impacting on immune functions at other sites. Key inflammatory mediators, including IL-6, TNF, IFNγ and VEGF[30] are raised in serum of IBD patients, as is

bacterial LPS[31] which may promote cytokine production via activation of immune cells at non-intestinal sites. Systemic effects, including increases in epithelial permeability[32] and up-regulation of neutrophil extravasation ligands on vascular endothelium, may lower the threshold for immune activation at extraintestinal sites. IBD associated cytokines, such as IL-23, which is produced at high levels in CD and UC, can activate immune cells resident within the synovial membrane and drive spondyloarthropathy.[33]

Systemic changes in innate immune function:

Exposure of neutrophils to inflammatory cytokines or other signals can enhance their response upon subsequent activation, a phenomenon termed neutrophil priming.[34] Circulating neutrophils show morphological evidence of activation in IBD[35] and are primed to produce increased levels of TNFα and IL-1β.[36] In contrast, recruitment of neutrophils to the skin and clearance of subcutaneous bacteria is reduced in patients with CD[37]. Likewise, changes in circulating monocytes[38] and macrophages derived from blood monocytes[37] have been reported in IBD, with reduced inflammatory cytokine production in response to bacterial stimulation.

Altered haematopoiesis:

Changes in circulating immune cells observed in IBD are likely to reflect altered haematopoiesis in the bone marrow. In mouse models, haematopoiesis is influenced by both microbial products[39-43] and the presence of intestinal inflammation.[44, 45] In IBD, systemic inflammatory cytokines, increased permeability of the intestine to microbial products or changes in the composition and metabolic products of the microbiota, could all influence the generation of innate immune cells.[46, 47]

Dysbiosis and gut microbiota

The long-established link between gut infections with enteric pathogens such as *Salmonella, Campylobacter, Yersinia* and *Shigella* and reactive arthritis is a clear indication that potential pathogenic pathways between microbiota in the gut and extraintestinal inflammation exist. Specific EIM are associated with gut dysbiosis: Patients with SpA have decreased faecal gut microbial diversity and increased abundance of *Ruminococcus gnavus* and genus *Dialister,* which positively correlated with disease activity.[48],[49] Patients with psoriatic arthritis also

exhibit decreased faecal microbial diversity.[50] In addition, faecal *Saccharomyces cerevisiae* abundance is decreased in psoriasis compared to healthy controls.[51]

PSC has also been associated with decreased faecal microbial diversity.[15, 52] One study has suggested that IBD patients have similar dysbiosis to IBD-PSC patients.[17] However, a conflicting report[53] makes it difficult to judge whether the risk for developing PSC is driven by specific microbial factors.[17] There is a paucity of studies determining gut dysbiosis in individuals with inflammatory eye disease, although one study demonstrated differences in gut microbiota between healthy individuals and those with age-related macular degeneration[54] and preliminary data suggested the existence of an intraocular microbiota.[55]

There is a range of potential mechanisms by which gut microbiota drive the pathogenesis of EIM (**Box 1**).

1. Molecular mimicry: similarity between gut microbiota and non-microbial epitopes present at the extraintestinal site
2. Microbial communities in the extraintestinal site: similarities with pro-inflammatory gut microbiota could drive extraintestinal inflammation
3. Microbial translocation: Microbiota or their components are translocated from the gut to the extraintestinal site, (e.g. to the liver via the portal circulation)
4. Soluble microbial derived factors: e.g. LPS may be released into the circulation and promote inflammation at extraintestinal sites.
5. Disruption of gut barrier: Specific microbiota such as mucin degraders may disrupt the gut mucosal barrier, facilitating leakage of cellular or non-cellular factors into the circulation
6. Microbiota-derived metabolites: e.g. metabolism of bile acids and generation of short-chain fatty acids which could both alter immune signalling
7. Acquisition of deleterious microbiota in early life resulting in altered immune development, which in turn generates a persistent pro-inflammatory immune “tone”

The first four of these hypothesized mechanisms have been included in the discussion in the preceding section. However, gut microbiota may promote inflammation at extraintestinal sites through metabolic activities. *Ruminococcus* which is altered in patients with arthritis could initiate breach of the intestinal barrier through mucin degradation.[56] In rats gut

microbiota-dependent alterations in bile acid deconjugation are associated with altered bile acid profiles in extraintestinal sites including kidney, heart, plasma and liver, demonstrating that gut microbial metabolic functions have the potential to influence immune signalling at distant sites.[57] Short-chain fatty acids (SCFA) produced by many gut bacteria may have metabolic or immunomodulatory effects. In experimental autoimmune uveitis oral administration of SCFA attenuated uveitis severity and was associated with suppression of effector T cell induction.[21] Furthermore, SCFA have a potential role in modulating T cell trafficking to extraintestinal sites. Finally it has been hypothesised that IBD linked dysbiosis may exert its pathogenic effect during immune development.[58] This is supported by animal models with bacterial colonisation of mice at age 3 weeks resulting in a persistent inflammatory tone, whereas colonisation at age 1 week did not.[59] Thus disruption of acquisition of gut microbiota early in life may generate persistent aberrant immune responses manifested in the gut or extraintestinally, or both. Indeed, factors that may influence the process of gut microbiota acquisition in early life such as breast feeding have been shown to be protective against the occurrence of ankylosing spondylitis (AS).[60]

Open questions:

1. Are the gut microbiota pathogenic in EIMs (via any of the mechanisms mentioned in the text) or are EIMs independent of gut microbiota?
2. If microbiota play a role, what is the mechanism?
3. If EIMs are driven by microbiota are these the same or different from those involved in IBD pathogenesis?
4. Are microbial communities in other parts of the body involved in IBD pathogenesis?

<u>Genetic basis of extraintestinal manifestations</u>

Familial and epidemiological evidence:

There is an extensive overlap in genetic risk loci for both IBD and EIM, particularly AS.[61] Association studies revealed a concordance in EIM present in 70% of parent-child pairs and in 84% of sibling pairs highlighting the role of genotype,[62] (or early life environmental factors). In addition, the appearance of one EIM increases the probability of developing other EIM.[1, 63] Further supporting the genetic underpinning of EIM, the CD risk gene NOD2, encoding a pattern recognition receptor, has also been associated with sacroiliitis,[64] and

uveitis.[65] Several HLA genes and HLA independent loci have been associated with the presence of EIM and a detailed description can be found in the Supplementary information. The genetic contribution to the pathogenesis of EIM and IBD comprises a combination of overlapping and independent loci, a situation which is consonant with the occurrence of EIM in individuals both with and without evidence of gut inflammation. However, whether the involved loci all contribute to pathology in an EIM-specific fashion, or whether there are genes that liberate inflammatory responses from restriction to specific body compartments and thus give rise to EIM in general, is not known.

Open questions:

1. Are the genes that predispose to specific EIM in IBD patients the same as the genes that predispose towards the EIM pathology in non-IBD patients?
2. Are there genes common to all EIM patients and distinct from non EIM IBD (immune mobility/ promiscuity factors)?
3. Do IBD patients with no EIM have protective factors i.e. they have the same genetic risk as EIM patients but have additional (genetic or environmental) protective factors?

<u>Animal models of EIM</u>

Animal models where inflammation is manifested at more than one anatomical site or bodily system (multifocal inflammation) provide experimental platforms to dissect pathogenic pathways of EIM and serve as tools to test potential therapies. However, only few models manifest multifocal inflammation, with colitis-arthritis models being the dominant phenotype available.

$TNF^{\Delta ARE}$ mice carry a genetic deletion of TNF AU-rich elements (ARE), leading to overexpression of TNF.[66] The resulting phenotype is CD-like transmural and granulomatous chronic ileitis along with spondyloarthropathy-like sacroiliitis, Achilles tendon enthesitis and peripheral arthritis. Paradoxically (given the importance of innate immune responses in human IBD), in this model ileitis appeared to be dependent on the presence of mature T and/or B cells, as mice with $TNF^{\Delta ARE}$ in combination with a RAG-/- background developed only arthritis.[66] Furthermore, mice with intestinal epithelial cell-specific TNF ARE deletion develop ileitis but not EIM,[67] indicating that intestinal inflammation *per se* is not sufficient

for induction of arthritis, which is therefore presumably dependent on local TNF production in the joint. Ileitis is abrogated in germ-free TNF$^{\Delta ARE}$ [68] and TNF$^{\Delta ARE}$/β7-/- mice,[69] but the effects of such manipulations on joint inflammation have not been reported yet. Taken together, in TNF$^{\Delta ARE}$ mice, gut and joint inflammation likely represent independent phenomena mediated by a common pro-inflammatory factor.

HLA-B27 transgenic rats develop spondylarthritis and colitis, but also gastritis, psoriasis and epididymitis.[70] In the intestinal mucosa there is increased production of pro-inflammatory cytokines (IFN-γ, IL-2, IL-1α, IL-1β, TNFα, and MIP2) and in addition plasma concentrations of TNFα and IL-6 are raised. IL-23 and IL-17A may play important roles, in association with HLA-B27 misfolding in the ER and activation of the unfolded protein response, leading to downstream inflammation.[71, 72] Interestingly, in this model both colitis and arthritis (but not dermatitis and epididymitis) are dependent upon the presence of microbiota.[73] The HLA-B27 model is consistent with a common genetic origin of multi-organ inflammation, but also emphasises the fact that some but not all EIM are dependent on microbiota. However, when interpreting data from germ-free models it is important to consider that conventionally reared mice are not only colonised with microbiota in the gut but also other organs such as skin, joints and eye which may also play a role in pathogenesis. More detailed experiments may be required to determine the contribution of extraintestinal microbiota communities in animal models of inflammation.

SKG mice that receive intraperitoneal injections of 1,3-β-glucan develop ileitis in association with enthesitis, arthritis, dactylitis, fasciitis, vertebral inflammation, and uveitis.[74] Treatment with anti-IL-23 mAbs or genetic deletion of the downstream cytokine IL-17A abrogate both ileitis and arthritis.[75] Time course expression studies identified intestinal mucosa as the source of elevated IL-23 production.[75] Nevertheless, immunological pathways of joint and gut inflammation in this model are not identical, as IL-22 neutralization reduced the severity of enthesitis but exacerbated ileitis in 1,3-β-glucan-treated SKG mice.

Animal models: Open questions

1. Could further animal models with intestinal inflammation and extraintestinal involvement (including sites other than joints) be developed?
2. Which common pathways between mucosal and extraintestinal inflammation are implicated in animal models where both occur?

3. What is the role of microbiota (including faecal transplant) in the development of inflammation in animal models?
4. Can animal models be used to elucidate the temporal relationship between intestinal disease and development of EIM?
5. How should animal models be used to investigate novel mechanisms and therapies such as neuroimmunomodulation?

Implications of the therapeutic effect of biologics and other treatments for EIM

Emerging data for the efficacy of biologics for the treatment of EIM may serve to expose underlying pathogenic mechanisms. Most evidence is available for anti-TNFα with good response rates for cutaneous manifestations, arthritis and ocular EIM. This has implicated TNFα-dependent mechanisms in EIM pathophysiology.[69-71, 76] However, anti-TNFα drugs are increasingly recognised to cause drug-induced skin lesions, contributing to the burden of skin disease in IBD.[77, 78] The pathogenesis of these lesions remains unclear; blocking TNFα may result in an imbalance of cytokines (for example, increased IFNα release, which can cause psoriasis)[79-81] and TNFα inhibition may lead to a reduced accumulation of Th1 and Th17 cells at the site of inflammation, but trigger a compensatory expansion at other locations.[82] Female gender and family history of inflammatory skin disorders were identified as risk factors which may also indicate a possible genetic predisposition for anti-TNFα induced skin lesions.[83]

The gut selective mechanism of the integrin α4β7 antibody vedolizumab should restrict its activity to the gut, since its counterpart MAdCAM1 is not expressed in the human skin.[84] The contribution of vedolizumab trials to understanding of EIM pathogenesis is complicated, since the evidence of its effect on EIM appears to be conflicting: One case series did not show any positive effect,[85] while a recent analysis from France suggested positive effects on EIM in most cases, but also revealed new onset of arthritis and paradoxical skin lesions.[86] The pathogenic mechanisms behind these observations remain elusive.[85] It may be speculated that a compensatory expansion of T cells at locations other than the gut could explain this phenomenon (similar to anti-TNFα induced lesions). On the other hand, a beneficial effect of vedolizumab on disease activity of EIM could occur if lymphocytes require the α4β7- MAdCAM1 interaction to gain access to the gut where they are activated,

followed by non-α4β7-dependent entry to extraintestinal sites. There is also evidence in animal models that some regulatory T cells require α4β7dependent entry into the gut to be educated before expressing their function elsewhere; vedolizumab could theoretically interfere with this.[87, 88] An alternative hypothesis is that α4β7 is directly involved in homing to extraintestinal sites as outlined above. It remains likely that vedolizumab has the capacity to illuminate pathogenic pathways in EIM.

Data on other biological agents are limited. So far, no trial has been published evaluating the anti-IL12/23 antibody ustekinumab in the management of EIM. Case series suggest it has efficacy in the treatment of anti-TNFα induced skin lesions,[89, 90] however, development of pustular psoriasis has been described.[91] Whether ustekinumab is effective in the treatment of non-drug induced EIM has yet to be determined. In contrast to anti-IL12/23 and despite the pathogenic role of Th17 cells in the development of colitis, trials with anti-IL-17A have failed in IBD with even higher adverse rates than placebo.[92] Moreover, in contrast to its efficacy in other inflammatory disorders, anti-IL-17A can even exacerbate IBD activity,[93] which highlights a distinct involvement of the IL-17A pathway in these entities. No data on JAK inhibitors is available so far, but upregulation of STAT3 in erythema nodosum and pyoderma gangrenosum[84] makes a response to JAK inhibitors reasonable to predict and sheds light on the possible involvement of the JAK-STAT pathway in cutaneous EIM.

Taken together, it is important that clinical trials and observational studies of biologic agents are designed to optimise the capture of data on effects on inflammation in other systems than the disease defined in the primary outcome.

Open questions:

1. How does vedolizumab affect EIM? Does it have the same effect on all EIM?
2. What is the implication of the overexpression of STAT for the prospect of using JAK-inhibitors for treating PG and EN?
3. How will EIM respond to IL12/23 treatment?

CLINICAL RESEARCH

Despite the presence of a wide range of EIM associated with IBD, standardized criteria for diagnosis, documentation or monitoring are lacking. Thus far only one randomized

controlled trial including IBD patients with EIM has been conducted.[94] Here we discuss the currently available paradigms and tools for clinical research in three of them: skin, joint and eye EIMs.

Diagnosis and monitoring of EIM

Because the diagnostic and monitoring tools for EIM have been developed within the organ-based specialities, this section is presented according to an organ-based structure.

Clinical criteria, indexes and scales

Joint manifestations:

IBD-associated joint symptoms may be subdivided into inflammatory and non-inflammatory joint pain, (arthritis and arthralgia respectively).[95, 96] Inflammatory arthropathies in IBD are the most common EIM and belong to the spondyloarthritis (SpA) group with a prevalence of 20-50% for axial inflammation,[97-99] and 5-20% for peripheral arthritis.[100, 101] The Assessment of SpondyloArthritis International Society (ASAS) developed classification criteria for both inflammatory axial and peripheral joint disease. These criteria are the current standard for clinical trials research and have good performance as tested against the rheumatologist's diagnosis (**Supplementary Figures 1 and 2**).[102-104] However, limited data evaluate ASAS criteria specifically in IBD patients. In IBD patients with inflammatory back pain ASAS criteria have an equivalent sensitivity but lower specificity compared to non-IBD patients.[105] This lower specificity may be due to the inclusion of IBD as one of the ASAS criteria of axial spondyloarthritis. Alternative classification tools such as the Amor classification[106] and the European Spondyloarthropathy Study Group (ESSG) criteria[107] also include IBD as a criterion, whereas the older Modified New York classification do not.[108] Nevertheless, in order to ensure applicability of research data to clinical practice it is advantageous that the definition of patient groups in clinical trials and research is consistent with that used rheumatology (i.e. ASAS criteria). Therefore, validation of these currently used tools in IBD patients should be carried out.

Monitoring tools for determining response to treatment and disease outcomes have also been developed by ASAS. The current gold standard tool for axial spondyloarthritis is the Ankylosing Spondylitis Disease Activity Score (ASDAS),[109] providing both a measurement of disease activity that may be followed over time as well as cut-offs to allow grouping of patients into different disease activity states (**Supplementary Figure 3**). ASDAS includes back

pain as one of the criteria. Hence, it is not well-adapted for use in the 5-20% of IBD patients with peripheral arthritis. In response to the lack of validated outcome measures in peripheral spondyloarthritis the authors of one randomized controlled trial of adalimumab in patients with non-psoriatic peripheral spondyloarthritis developed a new outcome measure, the Peripheral SpA Response Criteria (PSpARC40) measured after 12 weeks of treatment.[110] However, this outcome measure has not been widely applied and there is a need to validate the use of these tools in patients with multifocal inflammation.

Eye manifestations:

The most common eye EIMs are episcleritis and anterior uveitis. Scleritis and posterior or intermediate uveitis are rarer, but pose a greater potential risk to sight. **Supplementary Figure 4** summarizes some of the more common types of inflammatory eye disease as well as some of the ocular complications of IBD and its treatment. Episcleritis is usually treated topically with corticosteroids or non-steroidals. Uveitis may pose a greater diagnostic and therapeutic challenge. The SUN (Standardisation of Uveitis Nomenclature) classification is internationally acknowledged and as such research and clinical trials in uveitis in IBD patients should follow this system (**Supplementary tables 2-7**).[111, 112] SUN classification may be used both for diagnosis and classification of uveitis at presentation as well as for monitoring disease progression. However, it is relevant to consider that the SUN classification may have limitations especially for judging significance of the outcome of clinical interventions. The FDA defines a significant clinical response as 2-step change in parameters of the SUN classification, but many successful therapies do not meet the required 2 step improvement (especially in vitreous haze). Furthermore, the SUN classification describes anterior chamber cells as in unequal steps (0, +0.5, +1, +2 and +3) estimated subjectively by the consulting ophthalmologist which is therefore not optimal for quantitative research.

Skin manifestations:

Cutaneous manifestations are common in IBD patients[113] and include ectopic cutaneous IBD in addition to the other categories of pathologies as set out in **Table 1**. The diagnosis of cutaneous manifestations is principally based on clinical examination of the patient due to the inherently accessible nature of the skin. In atypical cases a skin biopsy is helpful.[114] In skin disorders, such as psoriasis and eczema specific indexes to objectively measure skin disease extent and activity have been developed (e.g. the Psoriasis Area Severity Index

(PASI)[115-117] and the Eczema Area and Severity Index (EASI)).[118] However similar standardised assessment techniques for cutaneous EIM of IBD such as EN and PG are lacking. The only randomised controlled trial of therapy for an EIM in IBD patients (infliximab for PG) employed a primary endpoint of clinical improvement at week 2, as determined by the clinician and patient's global assessment of reduction in ulcer size and depth and the degree of undermining of the ulcer edge.[94] Infliximab was shown to be superior to placebo, particularly in patients with disease duration ≤3 months. Standardisation of assessments methods such as that employed in this trial will enhance reproducibility in clinical research as well as facilitating meta-analysis of EIM research.

In summary, current tools for the diagnosis of EIM have for the most part been developed in patients with unifocal inflammation. Studies to validate the use of these tools in patients with multifocal inflammation, including IBD patients are needed. Even better would be a system of diagnosis and monitoring that reflects common pathogenic mechanisms which could then be applied to diseases generated by that common mechanism but manifesting in diverse clinical phenotypes.

Open questions:

1. Are tools for monitoring of unifocal inflammation valid for use in patients with multifocal inflammation?
2. If one of the criteria in an algorithm for diagnosing inflammatory pathology at an extraintestinal site is that the patient has IBD, will such an algorithm provide adequate diagnostic discrimination when applied to a population of IBD patients?
3. Is a single multidimensional scale for diagnosis and monitoring of inflammation at multiple sites possible? Is it desirable?

Biomarkers

There are no specific biomarkers for EIM activity in IBD with acute phase proteins ESR and CRP, leucocytosis, thrombocytosis and anaemia being non-specific and in addition ESR and CRP having low sensitivity being elevated in only 40-50% of patients with axial SpA. Conversely faecal calprotectin is only validated in the diagnosis and monitoring of gut inflammation and does not reflect disease activity at other sites.

Genetic markers for SpA:

Genetic factors may be utilised as biomarkers in the diagnosis of inflammatory pathology[119, 120]. Combining clinical factors with genetic data has been shown to be superior in predicting the development of EIMs compared to either alone. HLA-B27 positive IBD patients are at increased risk for developing AS.[2] Apart from HLA-B27, over 41 genes have been identified predisposing to AS.[121, 122] However, most of these have not been associated with increased risk for extra-articular inflammation. Currently there are neither reliable genetic biomarkers for peripheral SpA,[123 119, 124] nor for cutaneous or ocular EIM.

Imaging biomarkers for spondyloarthritis (SpA):

Traditional X-rays are of value in diagnosing axial SpA but only demonstrate changes in advanced cases. MRI usually demonstrates the first radiological changes in axial SpA and is - despite moderate sensitivity and specificity[125] - the imaging test of choice for detection of early disease[126-128] as well as the best objective technique to assess inflammatory disease activity.[129-134] This assessment has been standardised with the use of the Bath Ankylosing Spondylitis Radiology Index (BASRI).[135] In peripheral arthritis which is generally non-erosive, joint radiography is usually normal so ultrasonography is often employed to confirm the diagnosis. In addition, there is no evidence to confirm or refute the assumption that radiological findings in inflammatory arthropathy differ between patients with patients with only arthritis and those with inflammation also at distal sites.

Antimicrobial antibodies:

IBD is associated with the presence of antibodies to a variety of microorganisms such as anti-Saccharomyces cerevesiae antibodies (ASCA), antineutrophil cytoplasmic antibodies (ANCA), anti-I2 (associated with anti-Pseudomonas activity), anti-Escherichia coli outer membrane porin C (anti-OmpC) and anti-flagellin antibodies (anti-CBir1). Subclinical intestinal inflammation has been reported to be present in a significant proportion of patients with radiographic axial SpA.[136, 137] The data on the presence of these antimicrobial antibodies in patients with both IBD and SpA are inconsistent and mostly relate to axial SpA. Anti-I2 antibodies have been associated with the combination of AS and intestinal inflammation[137] as have antibodies against ASCA, anti-OmpC and anti-CBir1.[138]

Open questions:

1. Should patients with presenting with inflammatory pathologies be screened for multifocal inflammation?
2. Which biomarkers would be most appropriate for screening and in which populations?
3. Would biomarkers be useful to guide therapeutic decisions even in patients with unifocal inflammation (to reveal underlying mechanisms)?

Predictors and treatment of EIM

Predictors of EIM

The identification of patients at risk of EIM is desirable as this raises the possibility not only of treatment initiation prior to permanent tissue destruction, but even the potential for disease prevention. Moreover, patients in whom a propensity to develop inflammatory disease has already declared itself in one system may provide a unique opportunity for targeted screening in order to detect inflammation at distant anatomical sites. Several studies have investigated factors influencing the risk of developing EIM but with inconsistent results. This is likely caused by differences across studies regarding definitions and assessment of EIM as well as patient populations since only very few population-based studies exist. Furthermore, the occurrence and risk factors for EIM may also vary geographically.[139-141]

On the simplest level, demographic and clinical factors may be used to detect risk. For example, female sex,[29, 63, 113, 142-146] CD rather than UC,[113, 142, 143, 147, 148] increasing age,[29, 143, 149] long disease duration,[142, 143] colonic location in CD,[100, 143] extensive UC compared to proctitis,[142, 147] indicators of severe disease including need for steroids,[146] azathioprine,[146] biological therapy[29] or surgery,[100, 144, 148] and smoking both in CD[29, 148] and UC[29, 150] have all been associated with an increased risk for EIM. However, these associations are not reported consistently and are not replicated in all population-based studies[147-149] and as such, this approach may have limited applicability in clinical practice. Genetic factors play an important role in determining the presence of EIM,[119, 120] especially genes in the HLA region on chromosome 6 as described above.[151-153] Combining clinical factors with genetic data has been shown to be superior to predict the development of EIM compared to either alone.[119,

[124] Furthermore, specific features of the clinical presentation may alert the clinician to the potential for future EIM. For example, IBD is in the differential of any patient with ocular inflammation, especially in the "typical" constellation of bilateral anterior/intermediate granulomatous uveitis. Conversely, it is wise to monitor liver function tests especially in the IBD patient presenting with the clinical picture of mild, extensive colitis with rectal sparing and backwash ileitis, often associated with PSC.

Screening for IBD in patients with AS has been studied with some success, although the low rate of development of IBD in this group made the usefulness of screening somewhat questionable.[154] EIM are often tested for based on clinical suspicion however, screening for secondary diagnoses in patients with inflammatory pathologies has not yet proved a fruitful strategy.

Open questions:

1. Can accurate predictors of EIM be developed?
2. Once predictors are available: Can early intervention alter the future development of EIM?

Treatment

A recent systematic review by Peyrin-Biroulet *et al.* based on nine interventional studies, seven open label studies and thirteen non-interventional studies found a good clinical efficacy of adalimumab and infliximab for the treatment of musculoskeletal, cutaneous, and ocular manifestations, and some beneficial effect in metabolic bone disease and haematological or vascular EIM in IBD patients.[155] In contrast, no or limited efficacy of other biologic drugs including certolizumab pegol, golimumab, vedolizumab or natalizumab was identified. In this review however different ranges of pathology get grouped together, which may obscure the therapeutic effect for specific types of EIM that share a common mechanism.

Paradoxical, drug-induced EIM are well documented and hint at the complex effects that interference with immune function may have. This complexity is potentially compounded in patients with multifocal inflammation. The effect of vedolizumab, (which blocks α4β7 dependent migration of lymphocytes into the gut), on EIM has been difficult to predict, as

discussed above. Potentially vedolizumab may have no effect on extraintestinal inflammation due to its gut-selective nature; alternatively if lymphocytes causing extraintestinal inflammation require activation in the gut before migration to the distant site, then vedolizumab would be predicted to improve EIM. Lastly, if prevention of migration to the gut resulted in accumulation of lymphocytes at extraintestinal sites, then vedolizumab could cause exacerbation of EIM. Of course, it may be that each of these mechanisms is present in different patients. Another treatment strategy that may be examined in the future is combination therapy with biologics with different molecular targets, for example, combined anti-integrin/anti-TNFα therapy for IBD patients with EIM has shown some efficacy.[156]

It has been hypothesized that the extent of inflammation (for example the size of ulcerations in PG) may determine optimal drug dosing, with larger ulcers requiring higher doses of the drug.[94] However no dose-response studies and no RCTs have been presented in IBD-EIM patients during the induction phase of anti-TNFα treatment to determine optimal trough levels.[157] The concept of relating drug dose to total inflammatory burden has instinctive validity and could be potentially of great relevance to patients with EIM. However, this concept remains speculative at present and requires validation in clinical trials.[158]

Open questions:

1. Is there a dose-response relationship between anti-TNF therapy and EIM treatment response?
2. Are all anti-TNFα antibodies equally effective for the treatment of EIM?
3. Is there an additive effect of combined immunosuppression in IBD patients with EIM?
4. Are optimal anti-TNFα trough levels for IBD patients with EIM different from those for IBD patients without EIM?

<u>Treat to Target and Patient Reported Outcome Measures in EIM</u>

A “treat to target” strategy has been developed in many areas of medicine, where treatment outcomes are defined by specific objective endpoints. The concept driving this strategy is that traditional outcome measures fail to reflect subclinical, yet active disease, permitting the accumulation of tissue damage over time. With a treat-to-target strategy therapy is

intensified until the relevant evidence-based treatment target is in the desired range, which is associated with a reduction in end-organ destruction. For example in rheumatoid arthritis and scores such as the Disease Activity Score Calculator for Rheumatoid Arthritis (DAS-28) have been established.[159] This approach has also been used successfully in endocrinology especially in diabetes management.[160-162] Ongoing studies are developing this strategy in IBD.[163] Whether the same treatment targets developed for unifocal inflammation, can be applied (individually or perhaps in combination) in IBD-EIM or whether different targets should be developed, is unclear.

Another current advancement in the care of patients with chronic conditions is the development of Patient Reported Outcome Measures (PROM), which may themselves function as a treatment target. PROM are defined by the FDA as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else."[164] PROM may be disease specific such as the Inflammatory Bowel Disease Questionnaire (IBDQ-32),[165] the Inflammatory Bowel Disease Quality of Life Questionnaire (IBDQOL)[166] or the Work Productivity and Activity Impairment: Crohn's Disease (WPAI: CD).[167] The use of PROM designed for the assessment of unifocal inflammation in patients with multifocal inflammation presents obvious drawbacks, potentially missing significant aspects of the patient's experience. However, non-disease specific instruments have been developed such as the Short Form Health Survey[168] and the EQ-5D,[169] which may be more applicable in multifocal inflammation.

Open questions:

1. What are appropriate treatment targets for patients with multifocal inflammation?
2. Can established treatment targets from patients with joint, skin or eye disease be employed for patients with EIM in IBD?
3. Would there be a difference in how PROM and treat to target strategies function in patients with EIM activity that is synchronous with the IBD activity compared with patients with asynchronous disease activity?

CONCLUSION

Determining the mechanisms that cause inflammation to manifest unifocally or multifocally in different patients remains an enticing conundrum in immunology. Solving this conundrum may illuminate novel mechanisms and reveal a broader range of therapeutic targets. In the

context of the availability of a greater number of drugs targeted toward this broadening range of molecular targets, the previous organ-based approach to inflammatory disease may be inadequate. A holistic approach to the diagnosis and monitoring of inflammatory disease will allow a personalised therapeutic strategy. New tools for monitoring multifocal inflammation are needed in order to better capture the experience of the patient. This holistic approach to inflammatory disease requires greater cooperation between specialities and across research disciplines.

Figures

Figure 1. See separate document

Figure legend

Figure 1 Potential mechanisms of EIM

I Extension of immune responses from the intestine

A. Ectopic expression of adhesion molecules and chemokines *e.g. ectopic expression of MAdCAM-1 and CCL25 in the vascular endothelium of the portal tract*
B. T cell trafficking driven by non-specific adhesion molecules *e.g. α4β7-independent binding of leukocytes to the synovial membrane using a repertoire of adhesion molecules. Non-specific interactions may be initiated after low-grade inflammation, injury or mechanical stress*
C. Microbial antigen translocation *e.g. via portal tracts*
D. Microbial antigen cross reactivity *e.g. molecular mimicry between enteric bacteria and host MHC molecules*
E. Circulating antibodies *that may bind epitopes shared between human colon and extraintestinal tissues*

II EIM as independent inflammatory events

F. Shift in inflammatory tone *driven by genetic, environmental or microbial factors or by systemic increase in key inflammatory mediators*
G. Systemic changes in innate immune function *e.g. neutrophil priming*
H. Altered haematopoiesis *driven by microbial products, intestinal inflammation, systemic inflammatory cytokines, increased gut permeability, changes in the composition or metabolic products of the microbiota*
I. Gut microbiota drives distant inflammation *via microbial products such as LPS, through changes in gut permeability, microbiota-derived metabolites*

Tables

Table 1. Suggested categorisation of extraintestinal conditions that occur in IBD patients, (list of extraintestinal conditions associated with IBD adapted from Harbord *et al.*[2]).

System	A. Extraintestinal manifestations (multifocal inflammation)	B. Complications of IBD and its treatment	C. Associated conditions with uncertain mechanism
Joints and bones	Spondyloarthritis	Metabolic bone disease/ osteoporosis - (drug or nutritionally induced)	Non-inflammatory arthralgia
Eye	Uveitis Episcleritis Scleritis	Drug induced cataracts and other drug-induced and nutritional eye disease (see supplementary figure 4)	
Oral, aural and nasal	Oral CD Orofacial granulomatosis Metastatic CD		Sensorineural hearing loss
Skin	Erythema nodosum Pyoderma gangrenosum Sweet syndrome Metastatic CD	Drug-induced skin disease (e.g. anti-TNF induced psoriasis, DILE) Drug-induced skin cancer Drug hypersensitivity	Vitiligo Psoriasis Eczema Epidermolysis bullosa acquisita Cutaneous polyarteritis nodosa Hidradenitis

			suppurativa
Urogenital	Metastatic CD	Nephrolithiasis Amyloidosis Drug-induced tubulo-interstitial nephritis	
Hepato-pancreato-biliary	PSC	Portal vein thrombosis Hepatic amyloidosis DILI Drug-induced pancreatitis	Autoimmune hepatitis Granulomatous hepatitis Autoimmune pancreatitis
Neurological		Peripheral neuropathy (drug or nutritionally induced) Venous sinus thrombosis Stroke	Central demyelination
Cardiovascular		Ischaemic heart disease Cerebrovascular accident Mesenteric ischaemia	
Pulmonary		Drug-induced lung fibrosis	Inflammatory bronchial and parenchymal lung disease including asthma, bronchiectasis and interstitial pneumonias
Coagulopathy		Venous thromboembolism	
Endocrine		Drug-induced Cushing's and Addison syndromes Drug-induced diabetes	Type 1 diabetes Autoimmune thyroid disease

Infection		Infections including systemic and local secondary to immunosuppression Septic complications of IBD or surgery	

IBD: Inflammatory bowel disease, CD: Crohn's disease, DILE: Drug-induced lupus erythematosus, PSC: primary sclerosing cholangitis, DILI: Drug-induced liver injury

A. For several conditions there is evidence for a mechanistic link between two pathologies, as described by the definition put forward in this paper of a "true" extraintestinal manifestation (EIM) of IBD. We would propose that these conditions may also be considered multifocal inflammation.

B. Other conditions that occur in IBD patients are complications of the disease or its surgical or pharmacological management.

C. Several conditions occur more commonly in IBD patients but there is lack of evidence to categorise these as either complications or directly link them mechanistically to IBD. It is likely that as pathogenic mechanisms are better understood it may be possible to re-classify some of these conditions as "true" EIM/ multifocal inflammation.

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